

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/22, 9/52	A1	(11) International Publication Number: WO 97/25980 (43) International Publication Date: 24 July 1997 (24.07.97)
(21) International Application Number: PCT/US96/00512 (22) International Filing Date: 16 January 1996 (16.01.96) (71) Applicant: ADVANCED POLYMER SYSTEMS, INC. [US/US]; 3696 Haven Avenue, Redwood City, CA 94063 (US). (72) Inventors: BERLINER, David, L. ; 380 Selby Lane, Atherton, CA 94025 (US). NACHT, Sergio ; 409 Wembley Court, Redwood City, CA 94061 (US). (74) Agents: HEINES, M., Henry et al. ; Townsend and Townsend and Crew, Steuart Street Tower, One Market, San Francisco, CA 94105-1492 (US).		(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TOPICAL DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT (57) Abstract <p>Treatment of certain diseases of the colon by orally ingesting a suitable dosage form having a composition containing a plurality of rigid cross-linked polymer beads, each defining a substantially noncollapsible internal pore network, and a therapeutically effective amount of an active agent or drug in said pore network. The dosage form is treated with a polysaccharide, such as pectin, which is specifically attacked by colonic bacteria to permit drug release in the colon.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

TOPICAL DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT

5

This application is a continuation-in-part of patent application Serial No. 08/282,836 filed July 29, 1995.

BACKGROUND OF THE INVENTION

10 1. Field of the Invention

This invention relates to the treatment of diseases of the colon, such as inflammatory bowel disease. More particularly, it relates to a dosage form for an active agent and the method of its use in topically treating disease in the colon.

15

2. Description of the Prior Art

Many conditions either originate or are expressed in the lumen or tissue intermediate to the lumen of the gastrointestinal (G.I.) tract. One group of such conditions to which the present invention is directed are inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Current therapy methods for inflammatory bowel diseases usually use a formulation from which the drug is absorbed systemically even though the preferred site of action may be at or near the site of absorption. A relatively high systemic concentration is necessary in order to ensure an efficacy in local concentration of the drug. An example of this is the administration of prednisolone for inflammatory bowel disease. The steroid is given to elicit a local action but is absorbed systemically, which if continued for prolonged exposure may result in atrophy of adrenal glands or cause other side effects systemically.

20

25

30

Prodrug techniques have been used to prevent systemic absorption. This method requires a prodrug which is not absorbed and which undergoes a transformation to give the active species after passing the G.I. absorption window or zone for the active species. An example of this is the use of sulpha solazine for inflammatory bowel disease.

35

While the prodrug approach has worked for some drugs it is limited in scope due to its dependence upon the chemistry of the drug, prodrug, and G.I. environment. A new prodrug must be developed, if possible, for each active species.

SUMMARY OF THE INVENTION

The present invention circumvents the above problems by providing a method for treating certain diseases of the colon comprising (a) providing a dosage form containing a plurality of rigid cross-linked polymer beads, each defining a substantially noncollapsible internal pore network, and a therapeutically effective amount of an active agent in said pore network selected from the group consisting of corticosteroids and non-steroidal anti-inflammatory agents for treatment of inflammatory bowel disease, anti-tumor agents for treatment of colonic malignancies, anti-parasitic agents for treatment of parasites, and antibiotics for treatment of infections, said dosage form being treated to initially remain intact in the gastrointestinal tract, the treatment degrading in or near the large intestine whereby active agent is there released at a slow controlled rate; and (b) orally ingesting said dosage form.

The compositions used in the present method have been used as a delivery system for external topical skin administration and in such an environment have been shown to be capable of releasing an active substance at a controlled rate. It has now been found that such delivery systems utilizing the particular active agents herein described can be safely and efficaciously utilized internally of the G.I. tract and delivered to the desired location where the diseased tissue resides. Because the delivery systems release the active substances at a slow controlled rate systemic absorption is slowed or essentially prevented while at the same time a sufficiently high local concentration of the drug is provided to be effective in treating the disease. To the extent that some systemic absorption occurs with the corticosteroids, there is substantially no adverse side

effects because of the slow rate of systemic absorption and because the particular corticosteroids employed in this invention are either not adversely reactive in the body or are so rapidly metabolized in the body as to have no significant adverse impact.

In one preferred embodiment the dosage form is a pharmaceutical capsule or tablet containing the polymer beads with the selected active agent in their porous network. The active agent, such as a corticosteroid, will generally be present in each pharmaceutical capsule or tablet in the amount of 1-100 mg., frequently in the amount of about 5-20 mg.

Preferred polymer beads are formed from a copolymer selected from styrene-divinylbenzene and methyl methacrylate-ethylene glycol dimethacrylate, and have a diameter of about 5-200 microns, preferably about 10-40 microns.

The preferred embodiment also provides for control of the release zone of active ingredients at the desired site of action. For example, only the large intestine (a portion or its entire length) is affected in ulcerative colitis, whereas in Crohn's disease both the terminal ileum and the ascending colon are affected. In the preferred embodiment the selected dosage form is treated so that it will pass through preliminary stages of the G.I. tract and release active agent at the affected location. In the case of ulcerative colitis the dosage form is treated to initially remain intact in the G.I. tract and to degrade in or near the large intestine. Similarly, in Crohn's disease the dosage form is treated to initially remain intact in the G.I. tract until reaching the junction of the ileum with the colon and then degrades so as to release active agent in that location. This is accomplished by treating either the polymer beads, the dosage form, or both. For example, in one aspect of the preferred embodiment for treating Crohn's disease the polymer beads in the dosage form are coated with pectin. The corticosteroid is not released until enzymes normally present in the colon react with and remove the pectin so that entrapped corticosteroid is then released.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 plots the *in vitro* release of hydrocortisone from porous polymeric particles.

Figure 2 shows daily fecal dry weight of the three groups of rats used in the experiment of Example 4.

Figure 3 is a measurement of radioactivity in feces of the rats observed in the experiment of Example 4.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The beads or microspheres used in connection with the present invention are known in the art and are described in detail in U.S. patent No. 5,145,675 to Won, assigned to Advanced Polymer Systems. The disclosure of this patent is incorporated herein by reference. In particular, the present invention contemplates the use of co-polymers of styrene and divinylbenzene, the synthesis of which is disclosed in the above-referenced '675 patent in Example 1.1. The same example also illustrates a method for entrapping steroids within the porous network of the polymeric beads. Similarly, the present invention in the preferred embodiment contemplates the use of copolymers of methyl methacrylate and ethylene glycol dimethacrylate. Preparation of such co-polymer particles is described in the above referenced '675 patent in Example 6.2. Particles of the aforementioned types are commercially available from Advanced Polymer Systems of Redwood City, California, in the form of empty particles or as particles which have been loaded with the active agents utilized in the present invention.

As mentioned above, the polymeric particles containing the selected corticosteroid or other active agent may be treated to control the point in the G.I. tract that release of the active agent commences. In this regard, particles and/or the dosage form can be coated with enteric blocking agents which remain intact in the stomach where they are gastro resistant but which degrade in the intestines and are enterosoluble. Blocking agents suitable for use in the present invention are disclosed in U.S. Patent No. 5,316,774

for "Blocked Polymeric Particles Having Internal Pore Networks for Delivering Active Substances to Selected Environments."

One class of such materials suitable as enteric blocking agents are those which remain intact in the environment of the stomach but solubilize at the higher pH of the intestines. Materials of this type are known in the art where they have been used as coating for solid core drug formulations. The most effective enteric materials are polyacids having a pK_a of from about 3 to 5. Exemplary materials include fat-fatty acid mixtures, ethyl cellulose, cellulose acetate phthalates, and the like.

Also suitable as enteric coatings are various poly(meth)acrylates which may be introduced to the polymeric carrier particles or dosage form either by *in situ* polymerization or by absorption of an aqueous dispersion of the materials. Suitable poly(meth)acrylates include copolymers of methylmethacrylate and ethylacrylate as ester components with methacrylic acid which contain carboxylic groups that are transformed to carboxylate groups at a pH of from about 5 to 7. They are thus able to form water-insoluble materials which are resistant to gastric juices and methacrylate ester copolymers which are insoluble over the entire physiological pH range. Specific copolymers useful as enteric materials are as follows.

<u>Enteric Material</u>	<u>Molecular Weight</u>	<u>Preferred Monomer Ratio</u>
poly (methacrylic acid, ethylacrylate) copolymer	250 kD	1:1
poly (methacrylic acid, methylmethacrylate) copolymer	135 kD	1:2 to 1:2
poly (ethylacrylate, methacrylate) trimethylammoniaethylmethacrylate chloride	150 kD	1:2:0:2
poly (ethylacrylate, methylmethacrylate) trimethylammoniaethylmethacrylate chloride	150 kD	1:2:0:2

The present invention utilizes any suitable dosage form that can be used for oral drug delivery. In this regard the polymeric particles carrying the drug may be incorporated into a variety of known dosage forms, as described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton Pennsylvania, 16th Ed., 1982, the disclosure of which is incorporated herein by reference. The composition or formulation to be administered will contain a preselected quantity of the active substance(s) contained within the polymeric particles which are dispersed therein. Usually, a pharmaceutically acceptable non-toxic dosage form is prepared using conventional excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. Such compositions may be in the form of solutions, suspensions, tablets, pills, capsules, powders, and the like.

As noted above, the invention is directed to the treatment of four different types of diseases of the colon. In the preferred embodiment the dosage form and method is particularly suited for the treatment of inflammatory bowel disease. Preferred drugs utilized in the dosage form for treatment of inflammatory bowel disease include hydrocortisone, beclomethasone dipropionate, tixocortol pivalate, budesonide, dexamethasone, prednisone, prednisolone and triamcinolone acetonide. In addition to the preferred corticosteroids, non-steroidal anti-inflammatory agents are also contemplated, such as amino salicylate and sulfasalazine. In addition, other agents which have been found to beneficially treat anti-inflammatory bowel disease may be delivered by the present composition and method. For example, recent clinical studies have shown that ulcerative colitis may be beneficially treated with cyclosporine, a drug that has usually been given to transplant patients. Another class of drugs that is contemplated is referred to as prodrugs wherein they are entrapped in the polymeric particles in the same manner as the preferred drugs previously mentioned. Examples of prodrugs are dexamethasone-succinate-dextran

(Gastroenterology, 1994, 106:2 405-413), budesonide- β -D-glucuronide (Gut, 1994, 35: 1439-1446), and dexamethasone- β -D-glucuronide (Pharm Res, 1993, 10: 1553-1562).

With respect to the treatment of colonic malignancies, a suitable anti-tumor agent which is known in the art for the treatment of localized malignancies will be incorporated in the dosage form. Examples of anti-tumor agents suitable for use in this invention are methotrexate, 5-fluorouracil, and similarly functioning anti-neoplastic agents, such as tamoxifen, cyclophosphamide, mercaptopurine etoposide, indomethacin, semustine, fluorouracil, floxuridine and mitomycin. For the treatment of infections of the colon, antibiotics (including antibacterials) which are suitable for use in this invention include sulphanilamides and their derivatives, and other antibiotics specifically designed to treat particular bacterial infections associated with food ingestion. Additional examples include sulfonamides, norfloxacin, chloramphenicol, tetracyclines and vancomycin.

For treatment of parasites, suitable anti-parasitic agents include diloxanide furoate, metronidazole, quinacrine, tetracyclines, iodoquinol, dehydroemetine, amphotericin B, mebendazole and thiabendazole.

As noted, the key to obtaining release of the drug from the dosage form in or near the colon lies in the use of a coating that is not breached or significantly removed until reaching the colon where bacteria that are specific to and generally confined in the colon exist that attack and solubilize or otherwise remove the coating from the dosage form to permit release of the drug. In general, the coating may be on the polymeric beads or particles or on the exterior of the dosage form, whether it be a pharmaceutical capsule or tablet, or on both the polymeric beads and the dosage form. Where the dosage form is a tablet, "coating" of the polymeric beads or particles may be obtained by compressing a mixture of particles with the coating material. The term "coating" is thus used herein in a broad sense where the beads or dosage form are substantially surrounded by the "coating" material.

The substances used for the coating are carbohydrates, typically polysaccharides. In the preferred embodiment the polysaccharide is pectin. Polysaccharides useful as a coating are selectively degraded or otherwise solubilized only in the colon but not elsewhere in the digestive tract. Examples are pectin salts, chondroitin, cellulose, hemicellulose, and other sugars that are not degraded by digestive enzymes or otherwise absorbed before reaching the colon.

The amount of polysaccharide coating on the polymer beads or the dosage form will depend on the particular polysaccharide selected, but in any event will be of sufficient thickness to remain intact until reaching the colon. Thus, in the case of the preferred polysaccharide pectin, it has been shown that dissolution and release will depend on the particular pectin selected and primarily its methoxy content. Thus, pectins with a high degree of methoxylation demonstrate a higher degree of protection for the dosage form than those pectins with a lower degree of methoxylation. Pectin USP with a degree of methoxylation of 70% is an example of a preferred material which can be obtained from Bulmer Pectin, UK. The thickness of coating will depend on where it is placed in the dosage form. If the polymer particles themselves are coated, the thickness will be at the thinner end of the range, while a coating on the entire dosage form may be at the higher end of the range. A useful coating thickness range is from about .1 mm to about 1.0 mm.

The following Examples 1 and 2 illustrate the tablet dosage form (Example 1) and the capsule dosage form (Example 2) which may be used in this invention.

Example 1.Tablet Configuration

Tablets containing a suitable amount of a corticosteroid entrapped in a MICROSPONGE¹ System could be prepared with the following general formulation:

<u>Tablet Component</u>	<u>Weight</u>
MICROSPONGE [®] System with corticosteroid	250 mg
Pectin	200 mg
Dibasic Calcium Phosphate	100 mg
Eudragit 100S ²	100 mg
Magnesium Stearate	10 mg

Entrapment Preparation

Systems with corticosteroids are:

A) Hydrocortisone 10% in Acrylates Copolymer

(Formula per gram of entrapment)

Hydrocortisone	100 mg
Acrylates Copolymer (APS Type E 101 ³)	900 mg

This entrapment can be prepared as described in U.S. Patent No. 5,145,675. Namely, a 5% w/w hydrocortisone solution is prepared by adding 600 mg of hydrocortisone to 12 g of ethanol and then heated to 65°C. Small volumes of this solution (less than 1 ml) are then added to 4.5 g of blank polymer Type E 101 in an amber bottle and then slowly stirred using a spatula for several seconds. This is repeated until a total of 5 g of solution has been added. The bottle is capped and then

¹MICROSPONGE[®] - Registered trademark of Advanced Polymer Systems, Inc. of Redwood City, California, applied to its cross-linked microsphere polymer beads having an internal porous network.

²Eudragit 100S - poly(methylmethacrylate-co-methacrylic acid) blocking agent for enteric coating from Röhm Pharma GmbH, Darmstadt, West Germany.

³APS Type E 101, E 140 and E 104 - Polymer beads formed from a copolymer of methyl methacrylate-ethylene glycol dimethacrylate. From Advanced Polymer Systems, Inc., Redwood City, California. The polymers differ by particle size and porosity and all are within the range of about 8-25 microns in diameter.

placed on a roller mill for one hour to mix the contents. The polymer is then dried in an oven at 65°C for 2.5 hours. Due to the low solubility of hydrocortisone in the organic solvents used to prepare the entrapment, to achieve adequate levels of drug in the polymer to make it suitable for therapy, this process is repeated for a second entrapment step with drying of entrapped polymer in the oven at 50°C overnight.

B) Beclomethasone 5% in Acrylates Copolymer

(Formula per gram of entrapment)

Beclomethasone Dipropionate	50 mg
Acrylates Copolymer (APS Type E 140)	950 mg

A 2.5% w/w beclomethasone solution is prepared by adding 300 mg of beclomethasone to 12 g of ethanol and then heated to 65°C. Small volumes of this solution (less than 1 ml) are then added to 4.75 g of blank polymer in an amber bottle and then slowly stirred using a spatula for several seconds. This is repeated until a total of 5 g of solution has been added. The bottle is capped and then placed on a roller mill for one hour to mix the contents. The polymer is then dried in an oven at 65°C for 2.5 hours. This process is repeated for the second entrapment step with drying of entrapped microsphere polymer in the oven at 50°C overnight.

C) Budesonide 5% in Acrylates Copolymer

(Formula per gram of entrapment)

Budesonide	50 mg
Acrylates Copolymer (APS Type E 104)	950 mg

A 2.5% w/w budesonide solution is prepared by adding 300 mg of budesonide to 12 g of tetrahydrofuran and then heated to 65°C. Small volumes of this solution (less than 1 ml) are then added to 4.75 g of blank polymer in an amber bottle and then slowly stirred using a spatula for several seconds. This is repeated until a total of 5 g of solution has been added. The bottle is capped and then placed on a roller mill for one hour to mix the contents. The polymer is then dried in an oven at 65°C

overnight. This process is repeated for a second entrapment to obtain the desired payload.

Tablet Preparation

Tablets are prepared by mixing the indicated amount of polymer entrapment containing the drug and the other ingredients listed in the formulation, except the Eudragit. Tablets are produced by compression compaction using a stainless steel mold and a suitable hydraulic press.

These tablets are then pan-coated with the Eudragit 100S to provide an enteric coating that will allow the tablets to traverse through the stomach without disintegration or premature release of the drug. To coat the tablets, they are placed in a suitably heated rotating drum at about 40-45°C and, while rotating, an appropriate amount of an Eudragit solution in ethanol, isopropanol or acetone is slowly added to the tumbling tablets to obtain a uniform coating by evaporation of the solvent.

Example 2

Capsule Configuration

(Formula per Capsule)

MICROSPONGE® System with corticosteroid	250 mg
Pectin (or other suitable polysaccharide)	150 mg

Polymer containing the entrapped corticosteroid is prepared as described in Example 1 A), B) or C) above. A pectin solution is prepared by dissolving 1.5 g of pectin (moistened with 0.5 ml of ethanol to facilitate dissolution) in 30 ml of water heated to about 50°C. The suspension is maintained at this temperature with gentle stirring until a clear viscous solution is obtained. Then, 2.5 g of microspheres containing the corticosteroid is placed in a suitable glass or metal container such that it can be rotated while heated and its contents stirred to prevent agglomeration. The pectin solution is then added slowly and in small portions to the polymer, while rotating the vessel and continue heating. As the

mixture dries, more pectin solution is added until completion. A granular material, with granules about 0.6-1.0 mm in diameter is obtained. Larger clumps are easily broken into smaller particles with a glass rod or other suitable utensil.

The dry material thus obtained is divided into 400 mg portions and each is placed into a gelatin capsule. Alternatively, if smaller capsules are desired, 200 mg portions can be used.

These capsules, properly sealed, are then placed in a mildly heated coating pan (about 40°C) and, while rotating, an Eudragit 100S solution in ethanol, isopropanol or acetone is slowly added to the tumbling capsules to obtain a uniform coating when the solvent evaporates.

Similar examples of tablet or capsule configurations can be designed by using polymeric entrapments of other drugs like anti-tumor agents, antibacterials, etc., in MICROSPONGE Systems of different polymer compositions, particle size, and porosities as described in U.S. Patent No. 5,145,675.

The following examples will illustrate the safety of the present dosage form and method.

Example 3

In vitro Release of Hydrocortisone

Radiolabelled hydrocortisone was entrapped at a loading of 10% by weight in porous polymeric particles of methyl methacrylate-ethylene glycol dimethacrylate in which the particles had a diameter of about 25 μ m. The radioactively labelled hydrocortisone was entrapped in two steps using a 5% ethanolic solution at each step. Release of entrapped hydrocortisone at pH 7.5 was measured using a modified USP dissolution apparatus with a basket of 5 μ m mesh and a stirring speed of 150 rpm. Sixty percent of the entrapped hydrocortisone was released in the first two hours with a further 15% released over the next six hours. The dissolution rate of free radioactively labelled hydrocortisone

was also measured. The dissolution rate of free hydrocortisone was similar to the entrapped drug for the first two hours but total dissolution occurred in another six hours. The results of this comparative study are shown in Figure 1.

Example 4

This example demonstrates with animals the safety of the present dosage form when used internally of the body in the G.I. tract. A study was performed in rats in order to determine the time for total elimination of microsphere polymeric beads and the absorption of any extractable materials from the beads in rats after a single oral dose.

Three treatment groups were set up. Twelve rats were weighed and divided into quartiles. Each treatment group was randomly assigned to one rat from each quartile. The first treatment group (Group 1) were controls given 2 ml. of saline by gastric gavage. Group 2 rats were given 2 ml. of a saline slurry containing 200 mg of methyl methacrylate-ethylene glycol dimethacrylate copolymer beads (from Advanced Polymer Systems) radiolabelled with 2.6 million dpm ^{14}C . Group 3 rats were given a 2 ml saline slurry containing 200 mg of styrene-divinyl benzene copolymer beads (from Advanced Polymer Systems) radiolabelled with 2.6 million dpm ^{14}C .

Urine and stool were collected from each animal daily on the subsequent 7 days.

After 7 days autopsies were performed on all animals for gross anatomic observation and measurement of radioactivity. The only gross finding was in one animal from group 3 where polymer beads were observed in the pleural space. Radioactivity was found in this material (154,299 dpm/0.048) as well as in the lung (155 dpm/.099). Although not seen on gross exam, radioactivity was found in the lung of one animal from Group 2 (3299 dpm/.066 g) and esophagus (1388 dpm .58 g). These two animals represent technical errors in administering the polymer beads into the stomach. Thus, these animals were excluded from the graphs of the test results.

Radioactivity was measured in the following tissues and fluids for each animal: brain; testes; kidney; liver;

spleen; heart; lungs; esophagus; stomach; duodenum; jejunum; ileum; cecum; descending colon; blood; urine; and washing of stool material from the stomach, duodenum, jejunum, ileum, cecum, and descending colon. With the exception of the two animals described above, there was no radioactivity above control in any of the tissues or fluids.

The graph of Figure 2 shows the daily fecal dry weight in each of the three groups of rats. Analysis of variance is sensitive enough to show that fecal weight in the third group is different than the other two groups.

As expected, radioactivity was found in the daily fecal samples in the remaining rats. Figure 3 shows that most of the radioactivity appeared in the feces in the first day. The total calculated recovery of material was 110%, 100%, 95% (Group 2) and 93% 92%, 2% (Group 3).

There were two oddities in the fecal radioactivity measurements. One of the control rats had many counts in one of the fecal samples and one of the Group 3 rats excreted only 2% of radioactivity administered. In this animal there was not radioactivity in the organs or bowel. Thus, the finding was not due to retention of the material. There is no independent reason to reject these samples, and they remain in the reported results.

In conclusion, the data indicate that for both groups receiving radiolabelled microsponges there was rapid and complete elimination of the polymeric beads in the stool.

Example 5

Another study was conducted to determine the potential toxicity in rats of oral administration for 28 days using porous copolymeric particles formed from methylmethacrylate and dimethyl dimethacrylate made in accordance with Example 6.2 of the '675 patent. The empty particles were fed to rats by themselves and for comparison the same particles were fed in which the particles contained mineral oil in the pores. The conclusion of the study was that feeding of the two forms of the polymeric particles (with

and without mineral oil) did not demonstrate any deleterious effect on weight gain, food intake, or fecal output.

Example 6

Oral Dose Study of Polymeric Beads in Humans

5 The study was carried out in five subjects. In brief, each of the subjects collected all of his/her stool for one day before and either seven or nine days after ingesting a dose of ^{14}C -radiolabelled polymeric microspheres obtained from
10 Advanced Polymer Systems, Inc. The exact dose given was about 1 g containing 10 μCi of ^{14}C .

Each daily stool was dried at 60°C for at least one week followed by the determination of ^{14}C in each stool using a biological oxidizer that incinerated the stool in a stream
15 of N_2 and O_2 at 800°C . The resulting $^{14}\text{CO}_2$ was trapped in a scintillation cocktail and ^{14}C measured using standard liquid scintillation counting technique. The exact amount of ^{14}C in each stool was calculated using the weights of the samples oxidized, the weight of the total daily stool and the ^{14}C
20 measured in the oxidized sample.

Values for ^{14}C in each stool were expressed as a percent of the dose ingested.

The summary shows variability in the timing of excretion. However, it appears that except for subject C.R.,
25 all subjects excreted the dose by day six of the study (or five days after ingesting the dose). C.R. was unusual in that she did not have substantial excretion until four days after ingestion of the dose. She hadn't excreted all of her dose by day eight. This slow excretion and the fact that her stool
30 was not collected after day eight accounts for why she only excreted 91.97% of her dose -- a value less than all the other subjects.

The results in the table show that 98.76 ± 1.99 of the ingested doses were excreted in the five subjects.
35 Examination of the values indicates that they are not statistically significantly different from 100%. There was no radioactivity measured in the urine in any of the subjects tests.

In sum, the results demonstrated that ^{14}C -labelled polymeric microspheres were completely eliminated in the stool after oral ingestion. Furthermore, the peak of radioactivity in feces appeared between 48 and 72 hours after administration, indicating a slow transit through the G.I. tract.

Below in Table I is a summary of the results of the study.

Table I
Summary of Percent of Ingested Microspheres Excreted Per Day

S U B J E C T S						Mean \pm S.E.
	H.J.	C.R.	B.K.	L.N.	D.H.	
1	0	0	0	0	0	0
2	15.24	0	56.34	4.02	.04	23.87 \pm 9.57
3	74.55	.09	-	67.95	2.51	29.02 \pm 15.50
4	13.91	6.53	32.31	25.6	86.18	32.91 \pm 12.60
5	0.84	70.28	10.60	.015	7.53	20.43 \pm 13.04
6	0.03	8.78	3.03	.02	.87	2.55 \pm 1.48
7	.12	2.74	-.02	-.01	.08	0.58 \pm 0.48
8	.08	3.55	.03	.01	-.01	.73 \pm .63
9				-.02	-.01	-.015
10				.01	-.04	-.015
Total	104.77	91.97	102.29	97.58	97.21	98.76 \pm 1.99

Example 7

A study involving the gastrointestinal tract in subjects with ileostomy was conducted. The patients were all given a capsule similar to that described in Example 2 wherein the microspheres were loaded with ^{14}C -hydrocortisone.

In this study, ^{14}C -hydrocortisone was measured in both the urine and ileal effluent for 3-5 days after ingestion of a capsule containing the test material. In 3 of the subjects, the urine and ileal effluents were collected frequently so that the elimination of ^{14}C could be timed. The ileal effluents from one subject were accidentally destroyed during the drying process. Thus, only the data from four subjects can be evaluated.

The following are the percentages of ^{14}C recovered in the ileal effluent and urine for each of the evaluateable subjects. The first table shows recovery for the entire collection, while the second table shows the timing of the excretion in ileal effluent or urine.

Entire Collection

	<u>Percentage Recovered</u>	
	<u>Ileal Effluent</u>	<u>Urine</u>
Subject 1	53.8%	46.2%
Subject 2	98.0	2.0
Subject 3	(unable to evaluate)	
Subject 4	93.3	6.7
Subject 5	96.3	3.7
MEAN	85.4	14.6

Timed ExcretionPercentage Recovered

		<u>Ileal Effluent</u>		<u>Urine</u>	
5	Subject 1	0-24 hours	49.3%	0-24 hours	35.0%
		24-48	4.3	24-48	10.9
		48-72	0.3	48-72	0.4
10	Subject 2	0-14 hours	0.0%	0-22 hours	0.1%
		14-22	4.3	22-24	0.5
		22-25	85.8	24-29	0.9
		25-31	0.8	29-32	0.2
		31-38	3.4	32-36	0.1
		38-120	0.0	36-120	0.0
15	Subject 3	(unable to evaluate)		(unable to evaluate)	
20	Subject 4	0-3 hours	0.0%	0-3 hours	0.1%
		3-9	20.5	3-9	3.1
		9-16	71.5	9-16	2.4
		16-25	1.2	16-25	0.9
		25-96	0.0	25-32	0.2
				32-96	0.0
25	Subject 5	0-5 hours	0.5%	0-6 hours	0.0%
		5-16	93.5	6-10	0.3
				10-12	0.8
				12-22	1.4
		16-24	0.7	22-24	0.6
		24-28	0.3	24-30	0.2
		28-34	0.2	30-96	0.0
		34-48	0.3		
		48-72	0.6		
		72-96	0.3		

35 An examination of the entire collection results indicates that in three of the subjects the ^{14}C excretion was almost entirely in the ileal effluent. In one subject 53.8% of the ^{14}C was excreted by way of the ileal effluent. The reason for the difference between the results in this one

40 subject compared to the other three is not known.

 An examination of the timed excretion data for the ileal effluents indicates almost all of the excretion occurs within 24 hours after ingestion of the capsule. The exact timing within this 24 hours varied some between the three

45 subjects where such timing could be evaluated. In one, the ileal excretion was greatest at 22-25 hours after ingestion; in another it was at 3-16 hours; and in the third it was 5-16 hours. This variability may be due to differences in

residence time for the capsule in the stomach. The transfer of large particles from the stomach to the small intestine depends on many factors. One important factor is the relationship to meals. A capsule such as the one used in this study may not leave the stomach until all nutrients from meals have left the stomach and small intestine.

These results indicate that, in a normal individual (no ileostomy), the active ingredient would be released primarily in the colon, thus maximizing the therapeutic benefits of the drug and minimizing systemic absorption.

WHAT IS CLAIMED IS:

1 1. A dosage form for oral ingestion for treating
2 diseases of the colon comprising a pharmaceutical composition
3 containing a plurality of rigid cross-linked polymer beads,
4 each defining a substantially noncollapsible internal pore
5 network, and a therapeutically effective amount of an active
6 agent in said pore network selected from the group consisting
7 of corticosteroids and non-steroidal anti-inflammatory agents
8 for treatment of inflammatory bowel disease, anti-tumor agents
9 for treatment of colonic malignancies, anti-parasitic agents
10 for treatment of parasites, and antibiotics for treatment of
11 infections, said dosage form containing a polysaccharide to
12 initially remain intact in the gastrointestinal tract, said
13 polysaccharide degrading in or near the large intestine
14 whereby active agent is there released at a slow controlled
15 rate.

1 2. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said dosage form contains
3 an enteric blocking agent to protect against degradation by
4 acid conditions in the stomach.

1 3. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said dosage form is
3 treated to initially remain intact but with the treatment
4 degrading in or near the large intestine by surrounding the
5 polymeric beads with a polysaccharide that remains intact
6 until it is degraded by colonic bacteria to thereby release
7 said active agent in the colon.

1 4. A dosage form for treating disease of the colon
2 in accordance with claim 3, wherein said polysaccharide is
3 pectin.

1 5. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said active agent is
3 present in the dosage form in an amount of about 1-100 mg.

1 6. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said dosage form is
3 formulated for treating inflammatory bowel disease and said
4 active agent is a corticosteroid selected from the group
5 consisting of hydrocortisone, beclomethasone dipropionate,
6 tixocortol pivalate, dexamethasone, prednisone, budesonide and
7 prednisolone and triamcinolone acetonide.

1 7. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said dosage form is a
3 tablet, and the treatment of the tablet includes the addition
4 of a polysaccharide that remains intact until degraded by
5 colonic bacteria, said polysaccharide being compressed into
6 the tablet or coated thereon.

1 8. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said dosage form is a
3 pharmaceutical capsule with said polymer beads contained
4 therein and wherein the dosage form is treated with a
5 polysaccharide that remains intact until degraded by colonic
6 bacteria, wherein the polysaccharide is coated on said polymer
7 beads or on said pharmaceutical capsule.

1 9. A dosage form for treating disease of the colon
2 in accordance with claim 7, and including an enteric blocking
3 agent coated on said tablet as an exterior layer.

1 10. A dosage form for treating disease of the colon
2 in accordance with claim 8, and including an enteric blocking
3 agent coated on said pharmaceutical capsule as an exterior
4 layer.

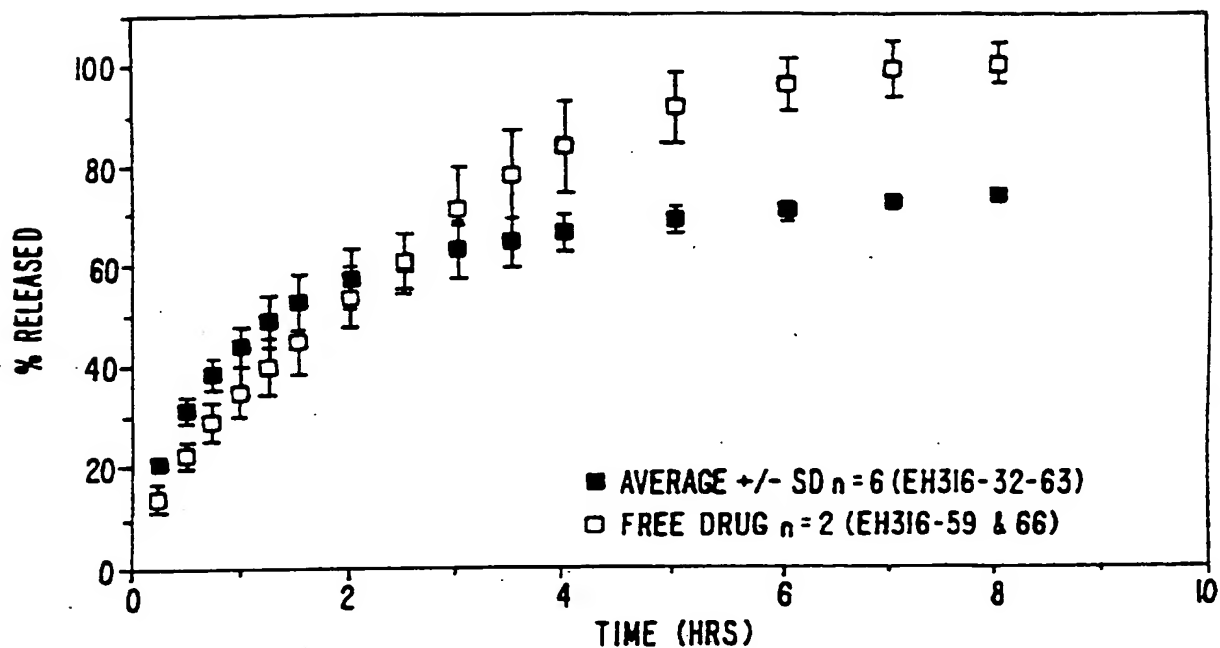
1 11. A dosage form for treating disease of the colon
2 in accordance with claim 1, wherein said polymer beads are
3 formed from a copolymer selected from the group consisting of
4 styrene-divinylbenzene and methyl methacrylate-ethylene glycol
5 dimethacrylate, and the selected polymer beads have a diameter
6 of about 5-200 microns.

1 12. A method for treating diseases of the colon
2 comprising: (a) providing a dosage form comprising a
3 pharmaceutical composition containing a plurality of rigid
4 cross-linked polymer beads, each defining a substantially
5 noncollapsible internal pore network and a therapeutically
6 effective amount of an active agent in said pore network
7 selected from the group consisting of corticosteroids and
8 non-steroidal anti-inflammatory agents for treatment of
9 inflammatory bowel disease, anti-tumor agents for treatment of
10 colonic malignancies, anti-parasitic agents for treatment of
11 parasites, and antibiotics for treatment of infections, said
12 dosage form being treated to initially remain intact in the
13 gastrointestinal tract, the treatment degrading in or near the
14 large intestine; and (b) orally ingesting said dosage form.

1 13. A method in accordance with claim 12 wherein
2 said disease of the colon is inflammatory bowel disease and
3 said dosage form is a pharmaceutical capsule containing said
4 polymeric beads.

1 14. A method in accordance with claim 13, wherein
2 said active agent is a corticosteroid selected from the group
3 consisting of hydrocortisone, beclomethasone dipropionate,
4 tixocortol pivalate, budesonide and triamcinolone acetonide
5 and is present in the dosage form in an amount of about 1-
6 100 mg.

1/2

**EXPERIMENTAL DETAILS:**

APPARATUS:	MODIFIED USP DISSOLUTION APPARATUS
DISSOLUTION MEDIUM:	50mM KH ₂ PO ₄ pH 7.5
D.M. TEMPERATURE:	37°C
STIRRING SPEED:	150 RPM
SAMPLE ANALYSIS:	SCINTILLATION COUNTING ON TRITIUM
POLYMERIC BEAD SAMPLE SIZE:	~110 mg
SAMPLE LOADING:	9.5% HYDROCORTISONE WITH [1,2- ³ H] HYDROCORTISONE
PARTICLE DIAMETER:	25 μm
FREE DRUG SAMPLE SIZE:	~10 mg HYDROCORTISONE WITH [1,2- ³ H] HYDROCORTISONE

FIG. 1.**SUBSTITUTE SHEET (RULE 26)**

2/2

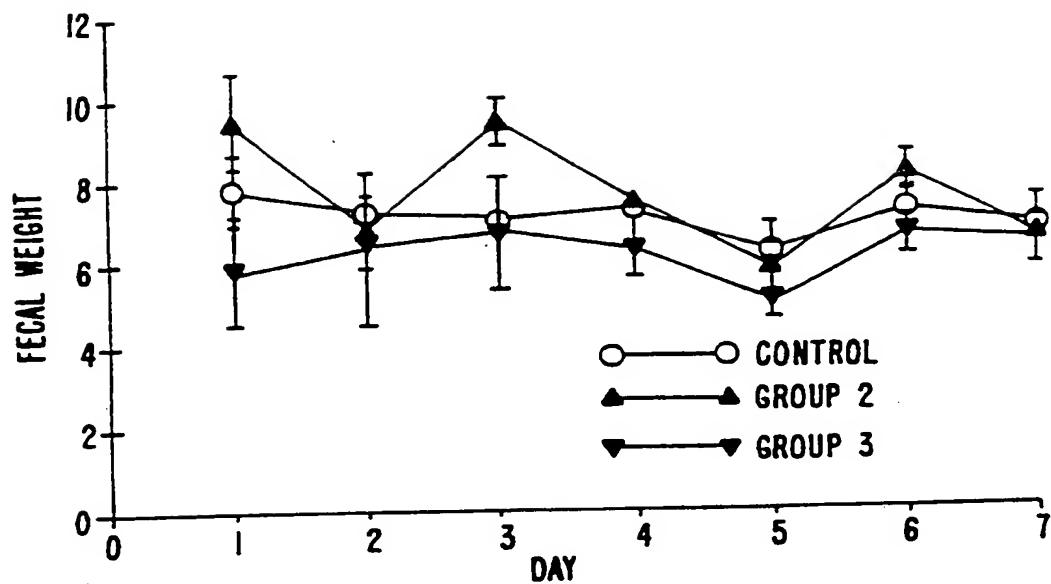


FIG. 2.

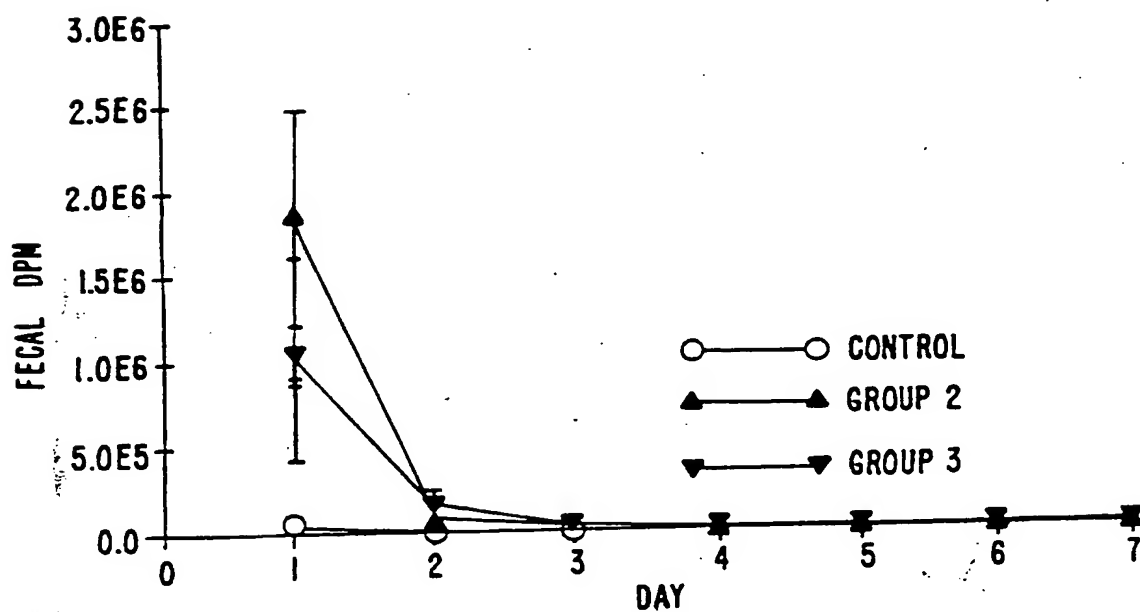


FIG. 3.

INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/US 96/00512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22 A61K9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,91 19483 (ADVANCED POLYMER SYSTEMS, INC.) 26 December 1991 see the whole document & US,A,5 316 774 cited in the application	1-14
Y	WO,A,91 16881 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUS.) 14 November 1991 see page 8, line 1 - line 19 see page 11, line 4 - page 12, line 26 see page 16, line 20 - line 29 see page 28, line 16 - page 29, line 28	1,3-8, 12-14
Y	DD,A,291 668 (BERLIN-CHEMIE AG) 28 February 1986 see the whole document	2,9-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

1 October 1996

Date of mailing of the international search report

18. 10. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+ 31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/00512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12 - 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00512

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9119483	26-12-91	AU-A- 8050791 DE-D- 69114006 DE-T- 69114006 EP-A- 0533799 US-A- 5316774	07-01-92 23-11-95 02-05-96 31-03-93 31-05-94
WO-A-9116881	14-11-91	AU-B- 660147 AU-A- 8087791 DE-T- 527942 EP-A- 0527942 ES-T- 2048133 HU-B- 210497 HU-A- 64210 US-A- 5525634	15-06-95 27-11-91 03-03-94 24-02-93 16-03-94 28-04-95 28-12-93 11-06-96
DD-A-291668		NONE	